

- This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims: Please amend the claims as follows:

We claim:

Claim 1. (Withdrawn) An isolated, modified hepsin molecule, or fragment or derivative thereof, comprising a substitute activation sequence.

Claim 2. (Withdrawn) The isolated molecule of claim 1, wherein the substitute activation sequence replaces a wildtype activation sequence RIVGG of FIG. 17.

Claim 3. (Withdrawn) The isolated molecule of claim 1, wherein the substitute activation sequence is DDDDKIVGG as shown in FIG. 18.

Claim 4. (Withdrawn) The isolated molecule of claim 1, having the amino acid sequence as shown in FIG. 18.

Claim 5. (Withdrawn) The isolated molecule of claim 1, wherein the substitute activation sequence is any one of SEQ ID NOS: 1-4.

Claim 6. (Withdrawn) The isolated molecule of claim 1, wherein the substitute activation sequence is recognized and cleaved by a protease.

Claim 7. (Withdrawn) The isolated molecule of claim 1, wherein the substitute activation sequence is recognized and cleaved by a serine protease.

Claim 8. (Withdrawn) The isolated molecule of claim 1, wherein the substitute activation sequence is recognized and cleaved by a type II transmembrane protease.

Claim 9. (Withdrawn) The isolated molecule of claim 1, wherein the

substitute activation sequence is DDDDK-IVGG (SEQ ID NO.: 3), which is recognized and cleaved by enterokinase.

Claim 10. (Withdrawn) The isolated molecule of claim 1, wherein the substitute activation sequence is recognized and cleaved by thrombin, clotting factor Xa, furin, trypsin, chymotrypsin, elastase, thrombin, plasmin, kallikrein, aerosin, human airway trypsin-like protease (HAT), mast cell tryptase, MBL-associated serine proteases (MASP-1 and MASP-2), corin, MT-SP1/matriptase, TMPRSS2 or Stubble-stubbloid.

Claim 11. (Withdrawn) The isolated molecule of claim 1, further comprising a signal peptide sequence.

Claim 12. (Withdrawn) The isolated molecule of claim 11, wherein the signal peptide sequence is bacterial, fungal, insect, plant, or animal.

Claim 13. (Withdrawn) The isolated molecule of claim 11, wherein the signal peptide is an Ig.kappa. signal sequence.

Claim 14. (Withdrawn) The isolated molecule of claim 1, further comprising an epitope tag.

Claim 15. (Withdrawn) The isolated molecule of claim 14, wherein the epitope tag is an amino acid tag.

Claim 16. (Withdrawn) The isolated molecule of claim 14, wherein the epitope tag is histidine or cysteine.

Claim 17. (Withdrawn) The isolated molecule of claim 14, wherein the epitope tag is V5 or flag.

Claim 18. (Withdrawn) The isolated molecule of claim 1, which is from a prokaryote or eukaryote source.

- Claim 19. (Withdrawn)** The isolated molecule of claim 18, wherein the eukaryote is a mammal.
- Claim 20. (Withdrawn)** The isolated molecule of claim 19, wherein the mammal is bovine, porcine, murine, equine, canine, feline, avian, piscine, ovine, insects, simian, or human animal.
- Claim 21. (Withdrawn)** An activated modified hepsin molecule, comprising a substitute activation sequence cleaved by a protease.
- Claim 22. (Withdrawn)** A method for detecting hepsin cleavage activity in a sample, comprising contacting the functionally-active hepsin molecule of claim 21 with a substrate under conditions so that the functionally active hepsin molecule cleaves the substrate and detecting the substrate cleavage products thereby indicating hepsin cleavage activity.
- Claim 23. (Withdrawn)** The method of claim 22, wherein the substrate is a chromogenic or fluorogenic substrate.
- Claim 24. (Withdrawn)** The method of claim 22, wherein the substrate is N-benzoyl-Leu-Ser-Arg-pNA.HCl, N-benzoyl-Ile-Glu-Phe-Ser-Arg-pNA.HCl, or N-benzoyl-Phe-Val-Arg-pNA.HCl.
- Claim 25. (Withdrawn)** The isolated, modified hepsin molecule of claim 1, wherein the substitute activation sequence has been cleaved thereby producing a modified activated hepsin molecule.
- Claim 26. (Withdrawn)** An isolated nucleic acid molecule encoding the modified hepsin molecule of claim 1.
- Claim 27. (Withdrawn)** A complementary nucleic acid molecule, comprising a nucleotide sequence complementary to the nucleic acid molecule of claim 26.

Claim 28. (Withdrawn) The nucleic acid molecule of claim 25 which is DNA or RNA.

Claim 29. (Withdrawn) The nucleic acid molecule of claim 26 which is a peptide nucleic acid molecule (PNA).

Claim 30. (Withdrawn) The nucleic acid molecule of claim 26 which is a phosphorothioate derivative molecule.

Claim 31. (Withdrawn) The nucleic acid molecule of claim 26 which is labeled so as to directly or indirectly produce a detectable signal with a compound selected from the group consisting of a radiolabel, an enzyme, a chromophore and a fluorescer.

Claim 32. (Withdrawn) A vector comprising the nucleic acid molecule of claim 26.

Claim 33. (Withdrawn) The vector of claim 32, wherein the vector is a plasmid, cosmid, BAC, YAC, PAC or a phagemid.

Claim 34. (Withdrawn) A host vector system comprising the vector of claim 32 in a suitable host cell.

Claim 35. (Withdrawn) The host vector system of claim 34, wherein the suitable host cell is a prokaryotic or eukaryotic cell.

Claim 36. (Withdrawn) The host vector system of claim 35, wherein the prokaryotic cell is a bacterial cell.

Claim 37. (Withdrawn) The host vector system of claim 35, wherein the eukaryotic cell is a yeast, plant, insect or mammalian cell.

Claim 38. (Withdrawn) The host vector system of claim 37, wherein the insect cell is Sf21.

Claim 39. (Withdrawn) A DNA sequence as depicted in FIG. 9, FIG. 10, or FIG. 11.

Claim 40. (Withdrawn) A method for detecting in a sample the presence of a nucleic acid molecule encoding a modified hepsin molecule, comprising contacting the sample with the nucleic acid molecule of claim 26 and detecting a complex formed between the nucleic acid molecule and a constituent in the sample or between the complementary nucleic acid molecule and a constituent in the sample, wherein the complex indicates the presence of the nucleic acid molecule encoding a modified hepsin molecule in the sample.

Claim 41. (Withdrawn) The method of claim 40, wherein the constituent is an RNA or cDNA molecule.

Claim 42. (Withdrawn) The method of claim 40, wherein the sample is a tissue, a cell, or a biological fluid.

Claim 43. (Withdrawn) The method of claim 42, wherein the biological fluid is urine, blood sera or phlegm.

Claim 44. (Withdrawn) The method of claim 42, wherein the sample is from prostate, liver, kidney, pancreas, stomach, thyroid, testes, or ovary.

Claim 45. (Withdrawn) A method for inducing an immune response in a subject, comprising administering the modified hepsin molecule of claim 1 to the subject.

Claim 46. (Withdrawn) A method for producing an antibody, comprising administering the modified hepsin molecule of claim 1 to a subject.

Claim 47. (Withdrawn) The method of claim 46 wherein the subject is a hepsin knock-out mouse.

Claim 48. (Currently Amended) An antibody, or fragment or derivative thereof, which binds to a modified hepsin molecule consisting of SEQ ID NO: 9.

Claim 49. (Original) An Fab, F(ab')₂ or Fv fragment of the antibody of claim 48.

Claim 50. (Original) The antibody of claim 48 which is a polyclonal antibody or monoclonal antibody.

Claim 51. (Original) A recombinant protein comprising the antigen-binding region of the antibody of claim 48.

Claim 52. (Original) An antibody which competes for binding to the same epitope as the epitope bound by the antibody of claim 48.

Claim 53. (Original) The antibody of claim 48 which is a chimeric antibody.

Claim 54. (Original) The antibody of claim 53, wherein the chimeric antibody comprises a human region and a murine region.

Claim 55. (Original) The antibody of claim 48 which is a humanized antibody.

Claim 56. (Original) The antibody of claim 48 which is a neutralizing antibody.

Claim 57. (Withdrawn) An idiotypic antibody of the modified hepsin molecule of claim 1.

Claim 58. (Original) An immunoconjugate comprising the antibody of claim 48 joined to a therapeutic agent.

Claim 59. (Original) The immunoconjugate of claim 58, wherein the therapeutic agent is a cytotoxic agent.

Claim 60. (Currently Amended) The immunoconjugate of claim 59, wherein the cytotoxic agent is selected from the group consisting of ricin, doxorubicin, daunorubicin, paclitaxel (TAXOL™), ethidium bromide, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin D, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, glucocorticoid and radioisotopes or a radioisotope.

Claim 61. (Currently Amended) A hybridoma which produces the antibody or the antibody fragment of claim 48.

Claim 62. (Original) A hybridoma deposited with the American Type Culture Collection and designated ATCC PTA-4561.

Claim 63. (Previously Presented) A hybridoma deposited with the American Type Culture Collection and designated ATCC PTA-5553.

Claim 64. (Previously Presented) A monoclonal antibody produced by the hybridoma of claim 61, 62, or 63.

Claim 65. (Previously Presented) A pharmaceutical composition, comprising the antibody of claim 64 and a suitable carrier.

Claim 66. (Withdrawn) A pharmaceutical composition, comprising the molecule of claim 1 and a suitable carrier.

Claim 67. (Currently Amended) The pharmaceutical composition of claim 65, wherein the suitable carrier is selected from the group consisting of a phosphate buffered saline solution, water, emulsion emulsions, oil/water emulsion, wetting agent agents, sterile solution, excipient solutions, excipients, starch, milk, sugar, clay, gelatin, stearic acid,

~~salt~~ a salt of stearic acid, magnesium stearate, calcium stearate, talc, vegetable fat or oil, gum, or glycol fat or oils, gums, and glycols.

Claim 68. (Previously Presented) The pharmaceutical composition of claim 65 which is formulated as a liposome, polymeric composition, or polymer microsphere.

Claim 69. (Previously Presented) The pharmaceutical composition of claim 65 which is formulated as a tablet, coated tablet, or capsule.

Claim 70. (Withdrawn) A method for binding a hepsin molecule, comprising contacting a sample with the antibody of claim 48 so as to bind the hepsin molecule.

Claim 71. (Withdrawn) A method for detecting a hepsin molecule, comprising contacting a sample with the antibody of claim 48 and detecting the binding of the antibody with the hepsin molecule in the sample.

Claim 72. (Withdrawn) The method of claim 71, wherein the detecting comprises determining whether a complex is formed between the hepsin molecule and the antibody, wherein the complex indicates the presence of the hepsin molecule in the sample.

Claim 73. (Withdrawn) A method for detecting the presence of hepsin molecule in a subject, comprising administering to the subject the antibody of claim 48, and detecting the binding of the hepsin molecule with the antibody with the hepsin molecule in the subject.

Claim 74. (Withdrawn) The method of claim 73, wherein the detecting comprises determining whether a complex is formed between the hepsin molecule and the antibody, wherein the complex indicates the presence of the hepsin molecule in the subject.

Claim 75. (Withdrawn) A method for diagnosing a cancer expressing hepsin in a subject, comprising quantitatively determining in a sample from the subject the

amount of a hepsin molecule using the antibody of claim 48, and comparing the amount of the hepsin molecule in a sample from a normal subject, the presence of a measurably different amount of the hepsin molecule between the sample from the subject and the sample from the normal subject indicating the presence of a cancer expressing hepsin in the subject.

Claim 76. (Withdrawn) A method for measuring the prognosis of a cancer expressing hepsin molecule in a subject, comprising quantitatively determining in a sample from the subject the amount of a hepsin molecule using the antibody of claim 48, and comparing the amount of the hepsin molecule in a sample from a normal subject, the presence of a measurably different amount of the hepsin molecule between the sample from the subject and the sample from the normal subject indicating the prognosis of the cancer expressing hepsin in the subject.

Claim 77. (Withdrawn) A method for monitoring the course of a cancer expressing hepsin molecule in a subject, comprising quantitatively determining in a first sample from the subject the amount of a hepsin molecule using the antibody of claim 48, and comparing the amount so determined with the amount of hepsin molecule present in a second sample from the subject, wherein the first and second samples are obtained from the subject at different points in time, a difference in the amounts of hepsin molecule in the first and second sample being indicative of the course of the cancer expressing hepsin molecule in the subject.

Claim 78. (Withdrawn) A method for inhibiting growth of a cell expressing hepsin molecule, comprising contacting the cell with the antibody of claim 48, so as to inhibit growth of the cell.

Claim 79. (Withdrawn) A method for killing a cell expressing hepsin, comprising contacting the cell with the antibody of claim 48 so as to kill the cell.

Claim 80. (Withdrawn) A method for inhibiting metastasis of a cancer cell expressing hepsin, comprising contacting the cancer cell with the antibody of claim 48.

Claim 81. (Withdrawn) A method for inhibiting angiogenesis of a cancer cell expressing hepsin, comprising contacting the cell with the antibody of claim 48.

Claim 82. (Withdrawn) The method of claim 78 or 79, wherein the cell is from a prostate, prostate cancer, metastasis of prostate cancer, liver, liver cancer, metastasis of liver cancer, kidney, kidney cancer, metastasis of kidney cancer, pancreas, pancreatic cancer, metastasis of pancreatic cancer, stomach, stomach cancer, metastasis of stomach cancer, thyroid, thyroid cancer, metastasis of thyroid cancer, testes, testicular cancer, metastasis of testicular cancer, ovary, ovarian cancer, or metastasis of ovarian cancer.

Claim 83. (Withdrawn) A method for producing an antibody that recognizes endogenous hepsin, comprising administering a modified hepsin molecule to a subject and producing the antibody.

Claim 84. (Withdrawn) A vaccine comprising the molecule of claim 1.

Claim 85. (Withdrawn) A kit comprising the nucleic acid molecule of claim 26.

Claim 86. (Previously Presented) An Fab, F(ab')₂ or Fv fragment of the antibody of claim 64.

Claim 87. (Currently Amended) The antibody of claim 64 which is a polyclonal antibody or monoclonal antibody.

Claim 88. (Previously Presented) A recombinant protein comprising the antigen-binding region of the antibody of claim 64.

Claim 89. (Previously Presented) An antibody which competes for binding to the same epitope as the epitope bound by the antibody of claim 64.

Claim 90. (Previously Presented) The antibody of claim 64 which is a chimeric antibody.

Claim 91. (Previously Presented) The antibody of claim 90, wherein the chimeric antibody comprises a human region and a murine region.

Claim 92. (Previously Presented) The antibody of claim 64 which is a humanized antibody.

Claim 93. (Previously Presented) The antibody of claim 64 which is a neutralizing antibody.

Claim 94. (Previously Presented) An immunoconjugate comprising the antibody of claim 64 joined to a therapeutic agent.

Claim 95. (Previously Presented) The immunoconjugate of claim 94, wherein the therapeutic agent is a cytotoxic agent.

Claim 96. (Currently Amended) The immunoconjugate of claim 95, wherein the cytotoxic agent is selected from the group consisting of ricin, doxorubicin, daunorubicin, paclitaxel (TAXOLTM), ethidium bromide, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin D, diphtheria toxin, *Pseudomonas* exotoxin (PE) A, PE40, abrin, glucocorticoid and ~~radioisotopes or a radioisotope~~.